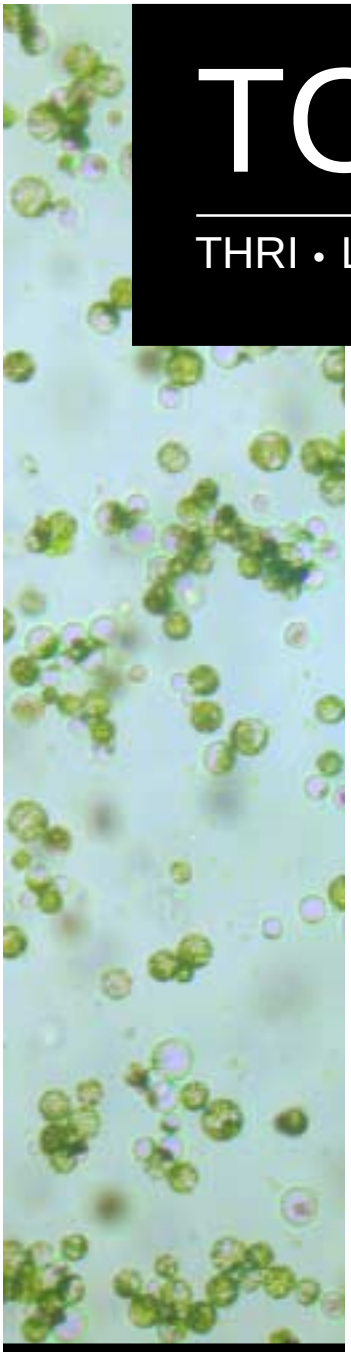

TOBACCO TECH

THRI • Looking to the Future of Tobacco • Issue 2, Jan. 2000

Tobacco "Bio-Prospecting"

A collaborative research project between the Tobacco and Health Research Institute (THRI) and the University of Kentucky Department of Chemistry and Department of Pharmacology is looking to the tobacco plant as a natural source of new drugs and other beneficial substances. Throughout history plants have been used to help treat and cure diseases, and they are now being reexamined as a source of possible cures for infections and diseases such as cancer and AIDS. Approximately 7,000 medical compounds prescribed by Western doctors are already produced or synthesized from natural plant materials. The anti-cancer drug Taxol™ from the Pacific Yew tree and the alkaloid Quinine extracted from the bark of the Cinchona tree for treating malaria are just two examples of beneficial plant-derived pharmaceuticals. Many companies now focus on the "bio-prospecting" of valuable materials from tropical rainforests, marine environments and other exotic sources. Every day researchers screen exotic plants from all over the world to assess their potential for producing a new drug.

But the THRI / University of Kentucky "bio-prospecting" effort is taking a different, more direct approach to finding beneficial substances in plants. All plants, including tobacco, are made up of thousands of different materials, and of the most abundant substances only a few are potentially useful as pharmaceuticals. However, there are also many minor compounds which are present below the detection limit of traditional screening procedures. This uncharted chemical territory may include substances with valuable pharmaceutical and other properties, but it is likely that these useful materials frequently go undiscovered on account of the relatively insensitive, cumbersome, and time-consuming screening methods which are conventionally applied.

The THRI research addresses these limitations and specifically targets the hidden metabolic potential of tobacco. First, the strategy amplifies the production of many of the minor compounds making the plant a new high-level source of natural materials. Through this process the tobacco plant, as well as other plants, can become its own "rainforest" to be explored and mined for all kinds of economically beneficial products.

Once the levels of the substances have been increased, it is still necessary to be able to determine which of those materials have potential as new drugs. To speed the discovery of these natural products, a novel part of the technology links the production of a fluorescent protein to the production of a particular class of compounds. Screening for active compounds is much more efficient through this focused process. Using the fluorescent protein as a "marker" provides a quick and easy way to determine if certain plant cells are overproducing the types of materials which are of interest. Simply shining an ultraviolet light on the plant allows the cells of interest to be identified from among thousands of other cells by the green fluorescent color that is produced.

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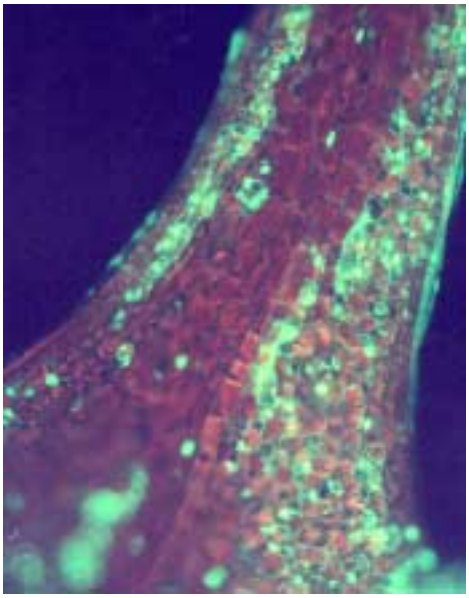
Bio-Prospecting

In tobacco, one class of compounds that is already of medicinal interest is the alkaloids. Nicotine is the most common alkaloid in tobacco species, but there are hundreds of others. These substances have shown potential in the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's. The fluorescent screening system now under development can be used to find new alkaloids which may have potential as drugs or to identify other valuable classes of compounds such as carotenoids or hormones.

The magnified leaf stem in the picture below shows a first step in setting up this detection system. In this test, normal cells will have a red color while the bright green illustrates where the expression of the fluorescent protein is the highest. In the bio-prospecting strategy, only those cells producing potentially useful drugs will emit a green light.

This bio-prospecting strategy has a very important implication for tobacco growers; the reliance on tobacco's own unique genes and metabolism means that if it is successful there is a very real possibility that the resulting new medical drugs *could only be produced by growing tobacco plants*.



New Tobacco Crops

To help tobacco become the crop of choice for the large-scale production of valuable materials in plants, THRI and the University of Kentucky College of Agriculture have recently scaled up their efforts to develop new tobacco varieties and production practices for "molecular farming." Advances on the scientific frontier continually push the boundaries of what is possible for these novel plant systems, making the production of materials such as pharmaceuticals or enzymes commercially attractive. Many companies have identified valuable product targets that could be produced in plants, but the emergence of new markets for growers has been hindered by the lack of accepted production practices and commercial scale process development. From an economic standpoint, optimizing production practices and developing tobacco varieties that are more suited for this type of production is essential as molecular farming moves from lab-scale production to a larger-scale commercial enterprise.

The production of these new types of tobacco will likely be quite different from traditional tobacco. The plants will be grown much closer together than normal to maximize the amount of harvested green leaf material per acre. The crop will also be harvested several times each year, requiring additional fertilization and making irrigation necessary. In addition, new varieties are being developed which could be direct seeded, yield higher levels of protein, better express new genes and have new traits such as herbicide and disease resistance. Close spacing and irrigation makes the engineering for blue-mold resistance particularly important, but THRI is also working on resistance to other diseases such as black shank and wildfire. Herbicide resistance is important for developing direct seeding because small tobacco seedlings have difficulty competing with significant weed pressure.

Establishing these efficient production practices is critical for making tobacco the most economical transgenic crop production system.

TOBACCO TECH is an occasional series published by THRI to inform growers and others about exciting new possibilities for tobacco. Topics will provide information on our cutting-edge biotechnology research program and our efforts to stimulate new crop opportunities for Kentucky tobacco farmers.